Randomised comparison of a simple warfarin dosing algorithm versus a computerised anticoagulation management system for control of warfarin maintenance therapy

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Summary
Excellent control of the international normalised ratio (INR) is associated with improved clinical outcomes in patients receiving warfarin, and can be achieved by anticoagulation clinics but is difficult in general practice. Anticoagulation clinics have often used validated commercial computer systems to manage the INR, but these are not usually available to general practitioners. It was the objective of this study to perform a randomised trial of a simple one-step warfarin dosing algorithm against a widely used computerised dosing system. During the period of introduction of a commercial computerised warfarin dosing system (DAWN AC) to an anticoagulation clinic, patients were randomised to have warfarin dose adjustment done according to recommendations of the existing warfarin dosing algorithm or to those of the computerised system. The study tested if the computerised system was non-inferior to the existing algorithm for the primary outcome of time in therapeutic INR range of 2.0–3.0 (TTR), with a one-sided non-inferiority margin of 4.5%. There were 541 patients randomised to commercial computerised system and 527 to the algorithm. Median follow-up was 159 days. A dose recommendation was provided and followed in 91% of occasions for the computerised system and in 90% for the algorithm (p=0.03). The mean TTR was 71.0% (standard deviation [SD] 23.2) for the computerised system and 71.9% (SD 22.9) for the algorithm (difference 0.9% [95% confidence interval: –1.4% to 4.1%]; p-value for non-inferiority=0.002; p-value for superiority=0.34). In conclusion, similar maintenance control of the INR was achieved with a simple one-step dosing algorithm and a commercial computerised management system.

Keywords
Clinical studies, clinical trials, oral anticoagulants, management of disease, stroke prevention, thrombosis

Introduction
Warfarin is the most widely used oral anticoagulant and is highly efficacious at preventing thrombosis, but is difficult to manage due to its narrow therapeutic range, many food and drug interactions, and inter-individual variability in dose response. Patients treated with warfarin must undergo coagulation monitoring to ensure that the international normalised ratio (INR) is maintained within a defined therapeutic range. A high time-in-therapeutic range (TTR) is associated with a superior antithrombotic efficacy and less bleeding, and is an accepted quality measure for warfarin maintenance therapy (1–4).

The 2012 American College of Chest Physicians (ACCP) guidelines suggest the use of dosing decision support, either computerised or manual, in preference to dosing without decision support (Grade 2C).(5) Community practices achieve on average an inferior TTR compared with specialised clinics, and they would be most likely to benefit from dosing decision support (6). Computer-assisted dosing systems produce better INR control than ‘care as usual’, but such systems are largely confined to specialised clinics due to their expense and complexity (7). No experimental evidence supports the use of a simple dosing algorithm. If shown to be effective, a simple, inexpensive dosing tool could assist healthcare providers in non-specialised settings to optimise anticoagulation control.

In 2008, a manual warfarin dosing algorithm was implemented to replace expertise-based (healthcare provider) dosing at the anticoagulation clinic, Hamilton Health Sciences – General Hospital. Introduction of this algorithm was associated with an improvement in the TTR for patients treated with warfarin (therapeutic...
INR target range 2.0–3.0) from 67.2% to 73.2%. A decision was subsequently made to introduce DAWN AC, a validated and commercially available computerised warfarin dosing system, and this provided an opportunity to compare the manual dosing algorithm with the computerised system (9–13).

Materials and methods

We performed a randomised controlled trial to test if the newly introduced computer system was non-inferior to the simple dosing algorithm already in use in the anticoagulation clinic, for the primary outcome of TTR (www.clinicaltrials.gov; NCT01024452). The Research Ethics Board of Hamilton Health Sciences approved the trial with a patient consent waiver based on the fact that the algorithm was already in routine clinical use in the clinic, the DAWN AC computerised system was validated to provide excellent INR control (9–13), and that an administrative decision had been made to introduce the computerised system.

Study setting and patients

All study patients were managed by the Hamilton General Hospital anticoagulation clinic, which has specialised non-physician healthcare personnel for patient education and follow-up, as well as for dosing warfarin with back up from hematologists. Prothrombin time measurements were performed according to usual practice at the laboratory of the Hamilton General Hospital. The International Sensitivity Index for conversion of prothrombin time to INR in this laboratory was 0.93. Patients were eligible for the study based on the following criteria: i) On warfarin maintenance therapy with an INR target range of 2.0–3.0; ii) At least three historical INR values were available including at least one value within the previous three months; iii) patients were using one of the three warfarin tablet strengths for which the algorithm was designed: 1 mg, 2.5 mg or 5 mg tablets.

Study design

In November 2009 the DAWN AC system was implemented, and patient data formerly recorded on dosing cards were entered into this system until January 2010. During this ‘wash in’ period: i) anticoagulation clinic personnel were trained and familiarised with the new computer system; ii) identified eligible patients were randomised to warfarin dosing with either the computer system or the algorithm, by anticoagulation clinic personnel in a 1:1 ratio using a computer-generated sequence with blocks of four. Dosing personnel were aware of treatment allocation, but patients were not. INR results and dosing details were recorded for both groups using the computer system, but for patients randomised to the dosing algorithm the system was programmed not to provide dosing recommendations. Study data were collected from February 1st to August 8th, 2010, and at study completion algorithm patients were transitioned to the DAWN AC system.

Computerised system

The DAWN AC anticoagulation software (4S Dawn Clinical Software: A Division of 4S Information Systems Ltd, Milnthorpe, UK. Version 7.8.1) uses a proprietary formula to determine the recommended warfarin doses and next INR test dates. DAWN AC also alerts users to overdue INR tests and provides reports for individual patients’ TTR. The program settings selected for the trial allowed dosing with half or whole pills and a maximum INR testing interval of four weeks to conform with the 2008 ACCP guidelines on anticoagulation management, which were valid at the time of the study (14).

Algorithm

The one-step algorithm used in this trial was originally based on physician expertise (Dr. S. Kaatz, Henry Ford Hospital, Detroit, MI, USA; personal communication) and was implemented in the anticoagulation clinic of the Hamilton General Hospital in the first half of 2008 (8). The algorithm uses only the existing weekly warfarin dose and current INR result to calculate the new weekly warfarin dose. The algorithm operates as follows: for INR 1.0–1.5 = increase weekly dose by 15%; for INR 1.5–2.0 increase by 10%; for INR 2.0–3.0 = no change in dose; for INR 3.0–4.0 = no change, but repeat INR in 1–2 weeks; for INR 3.0–4.0 (second time) decrease dose by 10% (see online Supplements 1-III, available at www.thrombosis-online.com). For this study we chose that the algorithm would not provide dose recommendations for INR values above 4.

Outcomes

The primary outcome was the mean of patients’ individual TTR, calculated per patient using linear interpolation with censoring of periods of >56 days between consecutive INRs or (temporary) warfarin discontinuation. Secondary outcomes included the mean INR value, time below INR of 2.0, time above INR of 3.0, time trend for monthly TTR (to assess for a potential learning curve for the newly introduced computerised system), mean interval between consecutive INR measurements, as well as TTR by following subgroups: age, gender, warfarin tablet strength, and primary warfarin indication.
**Sample size**

Patient enrollment was based on the following considerations. We assumed that the algorithm group would achieve a TTR of 73.2% (standard deviation [SD] 22.6), as previously reported in our clinic (8). A non-inferiority margin of 4.5% was considered clinically appropriate, to ensure that the computerised system achieved a TTR that is still better than the clinic’s previous documented expertise-based dosing (67.2%), as well as the minimum TTR which has been suggested as required to achieve clinical benefit from warfarin (65%) (1, 8). Based on these assumptions we calculated that a minimum of 800 patients were needed to have 80% power to conclude that the computerised system was non-inferior to the algorithm with a one sided type I error of 2.5%. As this study was somewhat opportunistic (based on the transition from the algorithm to the computerised system) we could not know what proportion of enrolled patients would have analysable results as patients can discontinue follow-up care by the thrombosis service at their discretion or due to physician preference. We chose to enroll 50% more patients than the estimated requirement.

**Statistical analysis**

Patients were included in the analysis if their data were considered analysable. This meant that i) they did not leave the clinic between the time of randomisation and February 1st when formal data collection was initiated, ii) their therapeutic INR target range remained at 2.0–3.0; iii) they continued to use a single warfarin tablet size of 1, 2.5 or 5 mg, and iv) that they had at least two consecutive INR values during the study period. The primary analysis for non-inferiority was performed using a two-group Student’s t-test to calculate a two-sided 95% confidence interval (CI) for the difference in TTR between the treatment groups (equivalent to a 97.5% one-sided CI). A z-score was used to describe the distance between the treatment group difference and the non-inferiority margin of 4.5%, which was summarised as a p-value. Comparisons of secondary outcomes and process measures were tested using independent Student’s t-test or Chi-square test. The consistency of the primary outcome in subgroups by age, gender, warfarin pill size, and primary warfarin indication was examined using linear regression with an interaction term for treatment and subgroup. A linear mixed model with an AR (1) correlation structure was used to test change in the monthly TTR trend over time by treatment group. Statistical analyses were performed using SAS version 9.1.

**Results**

A total of 1,298 patients were randomised; 648 to DAWN AC and 650 to the algorithm of whom 541 and 527 patients, respectively, were analysable and included in the primary analysis (Fig. 1). The mean age of the overall population was 68.6 (SD 13.7) years, 62.3% were male, the majority was using 2.5 mg or 5 mg tablets, and atrial fibrillation was the most frequent primary indication for warfarin, followed by aortic mechanical valve replacement (Table 1). The median follow-up period was 159 days (25th–75th percentile: 139–170), encompassing 155,535 patient days in total. There were a total of 7,401 days not included in the analysis due to either temporary warfarin discontinuation or to periods of >56...
days between INR measurements. The mean number of INR values per patient was 7.8 (SD 3.1).

Process of care

The study period included 4,194 INR values for DAWN AC and 4,151 for the algorithm, of which 75 and 83, respectively, were excluded because they immediately followed a period of warfarin interruption or more than 56 days (Table 2). The proprietary dosing approach of the computerised system occasionally does not make a dose recommendation (presumably due to insufficient or fluctuating data) and the simple algorithm was designed for this study not to make a specific dose recommendation for INR values over 4.0. Furthermore, clinic staff had the option to override a dose recommendation from both tools based on clinical judgment, i.e. not based on pre-specified study criteria. A specific warfarin dose was recommended and then followed in 91% of all INR dosing occasions for the computerised system and in 90% of occasions for the algorithm (p=0.03).

Figure 1 shows the distribution of INR values for which a dose recommendation was made and followed, and for which a recommendation was either not made or not followed. There was no obvious pattern regarding the absence of dose recommendations by DAWN AC according to INR values, except that no recommendations were given for INRs <1.3 (Fig. 2A). Algorithm recommendations were occasionally not followed when INRs were just below 2.0, and when they were 1.5 (Fig. 2B). When the algorithm recommendation was overruled, the dose increase was on average smaller than recommended for INRs <1.5 (+3% [SD 25] vs. +15% [SD 2]) and for INRs 1.5–2.0 (+3% [SD 11] vs. +10% [SD 2]), and the dose decrease for INRs 3.0–4.0 larger than recommended (–8% [SD 11] vs. –3% [SD 5]).

Primary analysis

The mean TTR for the computerised system was 71.0% (SD 23.2) and for the algorithm 71.9% (SD 22.9) (Fig. 3). The computerised system was non-inferior to the algorithm (mean difference 0.9%; 95% CI –1.4% – 4.1%; p-value for non-inferiority =0.002).

Secondary analyses

Patients randomised to the computerised system had a slightly lower mean INR than those randomised to the algorithm group (2.5 [SD 0.7] vs. 2.6 [SD 0.8]; p<0.0001), and computerised system patients spent more time with INR <2.0 (16.1% [SD 18.6] vs. 11.5% [SD 16.5]; p<0.001) and less time with INR >3.0 (12.9% [SD 16.7] vs. 16.2% [SD 18.8]; p=0.003) (Fig. 3). There were no differences for time spent with INR <1.5 (1.6% [SD 5.7] vs. 1.2% [SD 6.1]; p=0.28) and with INR >4.0 (1.8% [SD 6.9] vs. 1.8% [SD 5.5]; p=0.99) between DAWN AC and the algorithm, respectively. The time trends of the mean monthly TTR were similar between treatment groups (p-value for interaction between time and treatment: 0.68), and TTR remained stable over time for both groups. The effect of dosing method on TTR was consistent across all subgroups according to age, sex, warfarin pill size, and primary warfarin indication (p-values for interaction were 0.85, 0.46, 0.42 and 0.73, respectively).

Discussion

The main finding of this study is that the use of both a commercial computerised disease management system and a simple one-step algorithm provided excellent INR control, with a similar TTR of approximately 71% in a specialised clinic. The one-step algorithm could be a simple and effective warfarin maintenance dosing tool that may be of particular value for healthcare providers who do not have access to an anticoagulation clinic or to a computerised dosing system.

We previously demonstrated in an observational (before-after) study that the algorithm improved TTR compared with expertise-based dosing.(8) The present study is the first to evaluate any dosing algorithm in a randomised trial. The algorithm and the computerised system both helped physicians and patients achieve a TTR of greater than 70% which would be considered excellent al-

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Table 1: Patient characteristics. SD = standard deviation; TIA = transient ischaemic attack. * Mutually exclusive categories

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>DAWN AC</th>
<th>Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>68.7 (13.6)</td>
<td>69.1 (13.6)</td>
</tr>
<tr>
<td>Male</td>
<td>341 (63.0%)</td>
<td>326 (61.9%)</td>
</tr>
<tr>
<td>Pill size*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg</td>
<td>22 (4.1%)</td>
<td>27 (5.1%)</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>263 (48.6%)</td>
<td>226 (44.8%)</td>
</tr>
<tr>
<td>5 mg</td>
<td>256 (47.3%)</td>
<td>264 (50.1%)</td>
</tr>
<tr>
<td>Primary warfarin indication*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation / flutter</td>
<td>265 (49.0%)</td>
<td>244 (46.3%)</td>
</tr>
<tr>
<td>Aortic mechanical valve replacement</td>
<td>110 (20.3%)</td>
<td>127 (24.1%)</td>
</tr>
<tr>
<td>Other heart valve replacement</td>
<td>14 (2.6%)</td>
<td>17 (3.2%)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>53 (9.8%)</td>
<td>51 (9.7%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>36 (6.7%)</td>
<td>29 (5.5%)</td>
</tr>
<tr>
<td>Stroke / TIA</td>
<td>18 (3.3%)</td>
<td>20 (3.8%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>17 (3.1%)</td>
<td>15 (2.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (5.2%)</td>
<td>24 (4.6%)</td>
</tr>
</tbody>
</table>

TTR of greater than 70% which would be considered excellent al-

* SD = standard deviation; TIA = transient ischaemic attack. * Mutually exclusive categories.

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though some health care systems, especially in Northern Europe, have been able to achieve slightly better TTR results (16). The computerised system tested in this study (DAWN AC) is one of the most extensively studied and widely used computer anticoagulation management programs. Compared with ‘care as usual’, three studies reported improved maintenance TTR with the DAWN AC (11–13), but two others found no benefit (9, 10). Our patient group managed with DAWN AC had a higher TTR than the majority of patients in a recent large study, in which 13 centres using the DAWN AC system achieved a mean TTR of 66.6% (range 51.3 to 81.5%) and 19 centres using the PARMA system achieved a mean TTR of 65.7% (range 57.5 to 74.1%) (12, 13, 17). This indicates that the lack of a difference in TTR between the computerised system and the algorithm in our study was probably not due to suboptimal use of the system.

Although the two studied dosing methods had a very similar TTR, there were some differences in how this was achieved. DAWN AC was associated with a greater time with INR <2.0, while the algorithm had a greater time with INR >3.0. It is unlikely that these differences in time below and above INR range will lead to important differences in thrombotic and bleeding event rates. Firstly, no differences were observed for the more hazardous out-of-range INR values of <1.5 and >4.0. Second, only overall TTR is proven to be associated with patient outcomes, whereas an association between time <2.0 and stroke or time >3.0 and bleeding are less well established (1–4, 18). Nevertheless, an INR just below 2 may confer a greater risk of adverse events than an INR just above 3 (19). Our study was not powered to measure clinical outcomes.

In somewhat less than 10% of dosing occasions, the two systems either did not make a recommendation or the clinicians chose not to follow the dose recommended. DAWN AC was less likely to generate a recommended dose, but its recommendations were rarely overruled. The algorithm provided a dosing recommendation in more instances but was occasionally overruled for low INRs. It is unlikely that the latter contributed to the slightly higher mean INR and higher time above 3 for the algorithm patients, since dose increases for low INRs were smaller and dose decreases for high INRs larger than recommended. The high rate of adherence to the algorithm in this study indicates that this algorithm can be used safely by relatively inexperienced clinicians or supporting healthcare personnel. Still, clinical judgment should be used for both dosing methods, especially when no recommendation is provided, or when special situations arise such as missed doses, changes in concomitant medications, or changes in nutrition, and new comorbidities. Whether the algorithm could be used by patients in combination with point of care INR testing at home needs to be specifically tested.

The algorithm is attractive for use where computer-assisted dosing is not affordable, including in developing countries where cost effective methods of anticoagulation are needed and where TTR is often very low (16). Computerised systems such as the DAWN AC system will remain the preferred approach in high volume thrombosis services, since it provides alerts, calculates individual patient TTR, and serves as a database for clinic evaluation and research.

### Strengths and limitations

This is the first study to validate a manual dosing tool in a randomised fashion, and to compare it with a computer system. Nevertheless, there are some limitations. We conducted the trial at a single anticoagulation clinic with experienced specialised personnel and results are not necessarily transferable to less specialised healthcare settings. The turnover of patients in the thrombosis service was high and a substantial portion of patients did not complete the full trial period, although drop out was well balanced between groups. Adherence to dose recommendations was somewhat lower in the algorithm group, the computerised system provided recommendations for INRs >4 where the algorithm did not,

<table>
<thead>
<tr>
<th>Table 2: Warfarin management.</th>
<th>DAWN AC N=541</th>
<th>Algorithm N=527</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of study INR values</td>
<td>4194</td>
<td>4121</td>
<td></td>
</tr>
<tr>
<td>Included study INRs for analyses</td>
<td>4119 (98.2%)</td>
<td>4038 (98.0%)</td>
<td>0.4508</td>
</tr>
<tr>
<td>Mean number of INR values per patient (SD)</td>
<td>7.8 (3.0)</td>
<td>7.8 (3.1)</td>
<td>0.7210</td>
</tr>
<tr>
<td>Mean interval between INRs, days (SD)</td>
<td>20.8 (10.7)</td>
<td>20.3 (10.8)</td>
<td>0.0458</td>
</tr>
<tr>
<td>Mean weekly warfarin dose, mg (SD)</td>
<td>34.2 (17.0)</td>
<td>36.0 (18.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Warfarin dosing consistent with recommendations (adherence)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INRs with dose recommendation</td>
<td>3778 / 4119 (91.7%)</td>
<td>3855 / 4038 (95.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>INRs with dose recommendation and adherence to recommended weekly dose ± 0.5 pill</td>
<td>3758 / 4119 (91.2%)</td>
<td>3628 / 4038 (89.8%)</td>
<td>0.0320</td>
</tr>
</tbody>
</table>

INR = international normalised ratio; SD = standard deviation. *INR values following a period of temporary warfarin discontinuation or >56 days were excluded from all subsequent analyses, including the primary and secondary endpoint.
Figure 2: Frequency of dosing recommendations according to INR and adherence to dosing recommendation using DAWN AC (A) and the algorithm (B). A) * Since only 0.8% of DAWN AC dosing recommendations was overruled, the black bars primarily represent the number of occasions where no dosing recommendation was provided. B) * Specific dosing recommendations were provided by the Algorithm for all INRs <4.0 and no INRs ≥4.0. INR = International Normalised Ratio.
and dosing personnel were not blinded to the treatment allocation, which might have caused differences in dosing decisions when a recommendation by either method was not strictly followed or not provided. Finally, we did not measure clinical outcomes since this was not the purpose of the study, but there is good research evidence supporting the value of TTR as a surrogate outcome for patient important outcomes.

Clinical implications

The simple algorithm is a validated warfarin maintenance dosing tool that is easy to use and free of charge. Its high quality of INR control has been shown among specialised dosing personnel in the present study, but it might be of highest value for less specialised healthcare providers with smaller patient populations and without access to computer dosing.

Acknowledgements

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Conflicts of interest

None declared.
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